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⑳ **DEVICE FOR INSERTING IN WOUNDS AND WOUND CAVITIES.**

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Description

The invention relates to a device for inserting in wounds and wound cavities in humans and animals.

In the event of injury or after surgical intervention it may be appropriate or necessary to treat the wound or wound cavity with substances having an anti-bacterial and/or anti-toxic activity. This is particularly important if the wound is infected with bacteria and/or if bone tissue is affected by the infection. The treatment or osteitis or osteomyelitis is a problem to which there has not hitherto been a satisfactory solution. It is already known to implant bactericides in the bones. It is known, for example, to shape bone cement consisting of polymethylmethacrylate (PMMA) into a bead-like pellets which contain a bactericide (e.g. rifampicin). A number of these pellets are strung together with wire like a string of beads and implanted in the diseased bone so that the string or cord, possibly together with the outermost bead, projects and after some time the entire implant can be pulled out by means of this bead. However, the effectiveness of this implant leaves much to be desired. In US 3,948,524 a drug delivery device is claimed which, however, is only suited for being inserted in natural body cavities covered with epithelium and accessible from outside.

Taurolidine (4,4' methylen-bis(tetrahydro-2H-1,2,4-thiadiazin-1,1-dioxide)) has proved a particularly effective bactericidal substance. The bactericidal activity appears to be based on the destruction of the bacterial cell wall by the transfer of methylol groups whilst at the same time the lipopolysaccharides of the bacterial endotoxins and the proteins of the bacterial exotoxins are denatured and detoxified. In this way, toxic shock with the possibility of severe organ damage after anti-bacterial treatment can be avoided (cf. see Steinbach-Lebbin et al., Drug Research 32 (II), No. 12 (1982), 1542 to 1546). Taurolidine has relatively low solubility in water (about 1—2%). In view of its very good bactericidal properties (stronger than many antibiotics) and other properties (avoidance of bacterial resistance, local irritation or other undesirable side effects), attempts have been made to use solutions of taurolidine as bone rinses to combat and treat osteomyelitis. The activity is, however, of extremely limited duration.

The present invention relates to a device for inserting in wounds and wound cavities comprising a container containing a pharmaceutically active solid substance or a precursor therefor the walls of said container being formed, at least partially of a membrane which allows the active substance to escape into the wound area, characterized in that the pharmaceutically active substance is of low water solubility and in form of particles, and that the membrane comprises pores which are small enough to retain the particles within the container but do not restrict ingress of body fluids such that by simply retaining the particles of the substance, release of the

substance into the external body fluids is limited largely by water solubility and commonly achieves a zero-order release rate.

The term "wound" for the purpose of this invention relates to wound produced by trauma and/or surgical intervention but excludes incisions made solely for the implantation of a device of the type according to the invention containing an existing pharmaceutical active substance as distinct from a precursor thereof.

The term "wound cavities" for the purposes of this invention relates not only to artificially produced body cavities i.e. those produced by trauma or operation, but also natural body cavities or hollow organs, e.g. the thoracic cavity, abdominal cavity or the bladder, which may become wound cavities as the result of being opened up in an operation.

With the pharmaceutical container according to the invention it is possible to avoid the problems which arise in connection with wound treatment, particular the treatment of osteomyelitis or purulent peritonitis, such as limited duration of activity. The pharmaceutical composition located in the container according to the invention is released through the membrane not all at once but gradually frequently in constant quantities per unit of time, depending in part on its solubility. In this way, the substances can develop their activity in a controlled manner spread over a longer period. The pharmaceutical container according to the invention preferably contains pharmaceutical active substances having an anti-bacterial and/or anti-toxic activity, such as antibiotics, antiphlogistics, hormones or cortico-steroids, particularly with a view to use in the treatment of wounds and osteomyelitis, whilst, depending on the envisaged application, it is also possible to use mixtures of two or more active substances with identical, overlapping or different spectra of activity, e.g. two or more compounds of different solubility, which provide an additional means of controlling the release per unit of time and hence the duration of activity, or a combination of taurolidine and one or more antibiotics.

The pharmaceutical active substance taurolidine is particularly used in view of the intended purposes and the desired properties; as a result of its rather low solubility in water or body fluids this active substance is released only very slowly and therefore develops its bactericidal effect for as long as 3 to 4 weeks. Vaso-active and pH-regulating substances may also be used. When the container according to the invention, e.g. a dialysis tube containing the pharmaceutical active substance, is used in wounds and wound cavities, increased exudation is also found, which promotes the desired effect even further. If, on the other hand, the active substances, e.g. taurolidine, is introduced directly into the wound in dissolved form, after 3 to 4 hours it has all been washed out again, precisely because of this increased exudation, and its activity it thus rapidly terminated.

One advantage of the device according to the

invention is that it avoids local high concentrations of the active substance in contact with body tissues. In the case of taurolidine, 2% solutions have been known to give painful tissue reactions in some open wounds. A device according to the invention comprising particulate taurolidine contained in a dialysis tube permits concentrations of taurolidine to build up to levels of the order of 0.5% which do not give a painful reaction, while being quite adequate to kill any pathogens present, even difficult pathogens such as *Pseudomonas* species.

The device according to the invention may contain a solid or liquid pharmaceutical active substance; a solid active substance is preferably present in finely divided form, more particularly powdered, but depending on the membrane used it may also be used in solution, particularly in a physiologically compatible organic solvent which is difficultly soluble in water or only partly water-miscible.

The contents of the device according to the invention may also be precursors of the active substances (e.g. complexes, non-dialysible complexes, polymers) from which the actual dialysable active substance is formed by enzymatic or chemical reaction. The term "precursors" of the active substance for the purposes of the invention also refers to living cells, of human or other origin, preferably cells of connective tissue or bone which are able to release active substances to the surrounding medium.

Examples of such cells forming such a precursor include: histiocytes, plasma cells, mast cells, eosinophilic cells, pigment cells, white blood cells, the parent cells of white and red blood cells, cartilage cells including the formative and degraded forms, bone cells including the formative and degraded forms and fat cells. An advantage of this embodiment of the invention is the fact that the membrane, particularly when a semi-permeable membrane, protects the living cells from the body's immune system but allows the active substances, e.g. interleukins, to be released into the environment. This gives rise to new possible methods of treating diseases of the immune system, for healing bone fractures and the like.

The function of the membrane is to retain the main body of the active substance or precursor while releasing the active substance over a prolonged period. Where the active substance is a solid particulate material it may be sufficient for the membrane to possess pores (or other means permitting release of the substance) which are small enough to retain the particles within but do not restrict ingress of body fluids. By simply retaining the particulate active material, release into the external body fluids is limited largely by water solubility and commonly achieves a desired zero-order release rate. Where, however, it is desired to protect the main body of the active material, from components of the body fluids, notably enzymes, the membrane is desirably a semipermeable membrane, for example with a

cut-off in the region 50,000 Daltons. In general, semipermeable membranes provide a useful, relatively slow, release rate even where there is no need to prevent ingress of enzymes and are generally preferred.

The walls of the container according to the invention may consist wholly or partly of the said membrane, the container may be, for example, a plastics container consisting of a physiologically well-tolerated, sufficiently flexible plastics, e.g. a plastics tube, plastics sack or a preferably readily deformable plastics sphere which has one or more windows consisting of the said membrane; however, the container preferably consists of one or more tubes or hollow fibres consisting of a semi-permeable membrane and is in particular a dialysis tube, of the type which is commercially available. The use of a slightly flexible tube has the particular advantage that it can easily be inserted in the wound and removed again, it can fit the special shape of the wound or wound cavity, and, if necessary, can be coiled. Instead of a single tube it is also possible to use a bundle of hollow fibres containing the pharmaceutical active substance. Suitable plastics for the containers according to the invention include all the physiologically acceptable plastics which are suitable for implants (cf. for example *Angewandte chemie* 82, (1970) 367—379; 86I (1974) 145—150).

Semi-permeable membranes which may be used according to the invention may be natural and preferable artificial (semi-synthetic or synthetic) hydrophilic or hydrophobic membranes; all membranes which are used for artificial kidneys are particularly suitable; the membranes are preferably used in the form of hollow fibres and particularly tubes. Natural membranes include, for example, pigs bladders, fishes' swim bladders and intestines; artificially produced membranes are preferable those based on cellulose or cellulose derivatives such as, for example, regenerated cellulose (cellophane), parchment paper, colodion skins, cellulose acetate; or those based entirely on synthetic substances, e.g. polyethylene, polystyrene, polyacrylonitrile, polyacrylonitrile copolymers, N-methylpyrrolidone, coated onto polyethylene film, copolyetheresters such as polyethylene glycol/polyethylene terephthalate or silicones. The advantages of hydrophobic membranes such as silicone membranes include, in addition to their good compatibility with the tissue, their permeability to hydrophobic active substances such as corticosteroids. In the case of an aqueous cortisone solution, for example, such membranes prevent the water from passing through but not the cortisone. Hydrophilic membranes are suitable for hydrophilic active substances and let water through. Therefore, non-dissolved active substances may be used, which dissolve in the penetrating water of the tissues and diffuse out.

Preferably, the compatibility of the membranes with the blood is further improved by a known surface modification, such as membrane heparinisation; thus, ethyleneimine may be coated onto

cellulose membranes and then used to bind heparin, or cellulose acetate, e.g. cellulose acetate tubes or hollow fibres, may be deacylated with hydroxylamine, after which the heparin is bonded via bromocyanogen (cf. Hasenfratz and G. Knaup, *Artificial Organs*, Vol. 5. (Suppl.) 1981, 507—511). The layer thicknesses of the semi-permeable membranes which may be used according to the invention preferably range from 10 to 110 μm . The thickness of the tubes and the length of the tubes or bundle of hollow fibres is not critical and is determined particularly by the intended application (nature, form and size of the wound or wound cavity, etc) and also by the nature of the wall material; the thickness of the tube is generally from 0.3 to 2 cm.

In a particularly convenient embodiment of the apparatus according to the invention the container, e.g. dialysis tube, containing the pharmaceutical active substance is functionally combined with a tubular drainage device for draining wound secretions out of wounds or wound cavities. This combines the function of the device containing pharmaceutical active substance according to the invention (controlled release of the active substance over a fairly long period of time) with the function of the drainage device (draining off wound secretions and avoiding accumulations of secretions in wound cavities).

The drainage device may, theoretically, be any tubular drainage device conventionally used in surgery. Suction drainage tubes in which secretions are conveyed through the drainage tube under reduced pressure (less than atmospheric pressure) are particularly suitable. In addition to the better and safer discharge of the wound secretions, a further advantage of suction drainage tubes is that the wound cavities are reduced in size by the application of suction, provided that the resilient recoil forces of the tissues permit, thus more easily achieving the contact between the walls of the wound cavity required for healing.

The drainage tubes may consist of a physiologically compatible material conventionally used for such purposes, e.g. made of rubber or more preferably, plastics. The plastics material may be any physiologically acceptable plastics material conventionally used for these purposes (cf. *Angewandte chemie* 82, (1970) 367—379; 86I (1974) 145—150). The diameter and length of the drainage tubes depend on the intended purpose; the diameter is generally of the order of 0.5 cm. Preferably, the so called Redon drainage tube is used as the tubular drainage device, whilst a vacuum suction drainage tube is preferably used for festering wounds.

The drainage tube consists of a fairly rigid PVC tube about 0.5 cm in diameter and up to 1 m long, to which reduced pressure is applied.

For functionally combining the container containing the pharmaceutical active substance to the drainage device, one or more containers, preferably one or more semi-permeable membrane tubes, may be connected to the end of the

drainage device leading into the wound, e.g. with surgical sutures or by knotting the membrane tube; however, it is also possible for the container and drainage tube to be placed in the wound cavity separately but adjacent each other so that the drainage device performs the function of draining the secretions. A fixed connection between a tubular container according to the invention and the drainage tube has the advantage that both tubes can be pulled out of the wound together. In a preferred embodiment, the tube is a drainage device which contains over its entire length or part thereof, a semi-permeable membrane tube, e.g. a dialysis tube, which extends inside the tubular drainage device and projects out of the end inserted in the body to a suitable length for the intended purpose (size of the wound cavity) and extends into the wound cavity; the diameter of the drainage tube and dialysis tube should differ sufficiently to ensure that the secretions are properly drained off. In this embodiment the dialysis tube may be pulled out of the wound through the drainage tube or together with the latter.

In a particularly preferred embodiment, the tubular drainage device, particularly if it operates at reduced pressure, is constructed so that the end of the tube located in the body, i.e. against the wound, is split into several filaments ("frayed" rather like a horses tail or cauda drainage device) between which the liquid to be discharged can trickle in. The filaments may be formed as strips (e.g. by cutting into the end of the tube) or as fibres and by arranged side by side in a flat arrangement or in a bundle. The number of filaments is not critical; it is generally from 4 to 20, particularly from 8 to 12. The length of the filaments depends particularly on the envisaged use (e.g. the size of the wound cavity); it is generally between 5 and 20 cm.

In known improved embodiments of tubular drainage devices, such as a Redon tube, the end portion, i.e. the part of the tube adjacent to the wound, is provided with perforations which become larger and larger towards the end of the tube in order to improve the discharge of secretions; in another embodiment the drainage tube is provided with a spirally progressing groove. However, these drainage tubes have the disadvantage that they can only be pulled out of the wound by overcoming some resistance, particularly if suction is used, which will be painful for the patient. Moreover, the shape edged perforations or grooves may cause some tearing of tissue or coagulated blood when pulled out, thus causing fresh bleeding. These disadvantages can be avoided with the preferred embodiment of the drainage device according to the invention in which the section of tube located in the body ends in a plurality of filaments. These drainage tubes can be removed from the wound without any difficulty, with no pain, and no fresh bleeding.

The containers according to the invention, particularly membrane tubes, may be combined with the drainage tubes preferred according to the

invention in the manner described above, e.g. by securing dialysis tubes at the end of the drainage tube or by passing a dialysis tube through the drainage tube; however, it is advantageous to split the end into filaments because this enables the dialysis tubes to be fixed easily to the filaments, e.g. by knotting or by covering one or more filaments with the dialysis tubes, whilst maintaining the full draining effect.

The present invention therefore also relates to a tubular drainage device which is particularly suitable for combining with a container according to the invention having semi-permeable walls and containing a pharmaceutical active substance, this drainage device being characterised in that its end located in the body, i.e. at the wound, is split into several filaments, i.e. terminates in a plurality of filaments (cauda drainage).

Fig. 1 shows, by way of example, a device according to the invention consisting of drainage tube and dialysis tube, without restricting the invention thereto;

A drainage tube (1) has filaments (2) at its end which is inserted into the wound. Emerging from the end of the drainage tube is a dialysis tube (3) which is inserted in the wound; in the section of dialysis tube which is located in the wound there is a powdered pharmaceutical active substance, e.g. taurolidine (4); to retain the active substance, the dialysis tube is knotted or constricted (5).

Claims

1. A device for inserting in wounds and wound cavities, comprising a container containing a pharmaceutically active solid substance or a precursor therefor, the walls of said container being formed, at least partially, of a membrane which allows the active substance to escape into the wound area, characterized in that the pharmaceutically active substance is of low water solubility and in form of particles, and that the membrane comprises pores which are small enough to retain the particles within the container but do not restrict ingress of body fluids such that by simply retaining the particles of the substance, release of the substance into the external body fluids is limited largely by water solubility and commonly achieves a zero-order release rate.

2. Device as claimed in claim 1 in which the membrane is a semipermeable membrane.

3. Device as claimed in claim 2, characterised in that the container is a tube consisting of the semi-permeable membrane or it is a bundle of hollow fibres.

4. Device as claimed in claim 3, characterised in that the container is a dialysis tube.

5. Device as claimed in one of claims 1 to 4, characterised in that it contains the pharmaceutical active substance in powder form.

6. Device as claimed in one of claims 1 to 5, characterised in that it contains the pharmaceuti-

cal active substance in the form of a precursor therefor and the active substance is formed by a chemical or enzymatic reaction inside or outside the device.

7. Device as claimed in claim 6 characterised in that it contains, as the precursor form of a pharmaceutical active substance, living cells, particularly cells of connective tissue.

8. Device as claimed in one of claims 1 to 6, characterised in that the pharmaceutical active substance is a substance with anti-bacterial and/or antitoxic activity.

9. Device as claimed in one of claims 1 to 6, characterised in that the pharmaceutical active substance is taurolidine.

10. Device as claimed in one of claims 1 to 9, characterised in that it additionally contains a tubular wound drainage device operatively connected to drain away wound secretions from wounds and wound cavities.

11. Device as claimed in claim 10, characterized in that the end of the tubular wound drainage device which is located in the body is split into several filaments.

Patentansprüche

1. Vorrichtung zum Einsetzen in Wunden und Wundhöhlen, bestehend aus einem einen pharmazeutischen Wirkstoff oder dessen Vorstufe enthaltenden Behälter, wobei die Wände dieses Behälters zumindest teilweise von einer Membran gebildet werden, die es dem Wirkstoff ermöglicht, in das Wundgebiet auszutreten, dadurch gekennzeichnet, daß der pharmazeutische Wirkstoff eine geringe Wasserlöslichkeit besitzt und in Form von Teilchen vorliegt, und daß die Membran Poren aufweist, die klein genug sind, die Teilchen im Behälter zurückzuhalten, aber den Eintritt von Körperflüssigkeiten nicht zu beschränken, derart, daß durch einfaches Zurückhalten der Teilchen des Stoffes dessen Abgabe an die Körperflüssigkeiten auf der Aussenseite weitgehend durch die Wasserlöslichkeit begrenzt ist und im allgemeinen eine Abgabegeschwindigkeit nullter Ordnung erreicht wird.

2. Vorrichtung nach Anspruch 1, worin die Membran eine semipermeable Membran ist.

3. Vorrichtung nach Anspruch 2, dadurch gekennzeichnet, daß der Behälter ein aus der semipermeablen Membran bestehendes Rohr oder ein Bündel von Hohlfasern ist.

4. Vorrichtung nach Anspruch 3, dadurch gekennzeichnet, daß der Behälter ein Dialyserohr ist.

5. Vorrichtung nach einem der Ansprüche 1 bis 4, dadurch gekennzeichnet, daß sie den pharmazeutischen Wirkstoff in Pulverform enthält.

6. Vorrichtung nach einem der Ansprüche 1 bis 5, dadurch gekennzeichnet, daß sie den pharmazeutischen Wirkstoff in Form einer Vorstufe dafür enthält und der Wirkstoff durch eine chemische oder enzymatische Reaktion innerhalb oder außerhalb der Vorrichtung gebildet wird.

7. Vorrichtung nach Anspruch 6, dadurch gekennzeichnet, daß sie als Vorstufenform eines Wirkstoffs lebende Zellen, insbesondere Bindegewebszellen, enthält.

8. Vorrichtung nach einem der Ansprüche 1 bis 6, dadurch gekennzeichnet, daß der pharmazeutische Wirkstoff ein Stoff mit antibakterieller und/oder antitoxischer Wirksamkeit ist.

9. Vorrichtung nach einem der Ansprüche 1 bis 6, dadurch gekennzeichnet, daß es sich bei dem pharmazeutischen Wirkstoff um Taurolidin handelt.

10. Vorrichtung nach einem der Ansprüche 1 bis 9, dadurch gekennzeichnet, daß sie zusätzlich eine rohrförmige Wunddrainageeinrichtung enthält, die wirkverbunden ist, so daß Wundsekretionen aus Wunden und Wundhöhlen abfließen können.

11. Vorrichtung nach Anspruch 10, dadurch gekennzeichnet, daß das Ende der rohrförmigen, im Körper befindlichen Wunddrainageeinrichtung in mehrere Fäden gespalten ist.

Revendications

1. Un dispositif destiné à être introduit dans des plaies ou des cavités de plaies comprenant un récipient contenant une substance solide active d'un point de vue pharmaceutique ou un précurseur de substance active, les parois dudit récipient étant formées, au moins partiellement, d'une membrane qui permet à la substance active de se libérer dans la région de la plaie, caractérisé en ce que la substance active d'un point de vue pharmaceutique a une faible solubilité dans l'eau et est sous forme de particules, et en ce que la membrane comprend des pores qui sont suffisamment petits pour retenir les particules à l'intérieur du récipient mais qui ne limitent pas l'entrée des liquides d'origine corporelle de telle façon qu'en retenant simplement les particules de la substance, la libération de la substance dans les liquides externes d'origine corporelle est grandement limitée par la solubilité dans l'eau et atteint généralement un taux de libération de l'ordre de zéro.

2. Un dispositif selon la revendication 1, caractérisé en ce que la membrane est une membrane semi-perméable.

3. Un dispositif selon la revendication 2, caractérisé en ce que le récipient est un tube composé de la membrane semi-perméable ou en ce qu'il est un faisceau de fibres creuses.

4. Un dispositif selon la revendication 3, caractérisé en ce que le récipient est un tube de dialyse.

5. Un dispositif selon l'une des revendications 1 à 4, caractérisé en ce qu'il contient la substance active d'un point de vue pharmaceutique sous forme de poudre.

6. Un dispositif selon l'une des revendications 1 à 5, caractérisé en ce qu'il contient la substance active d'un point de vue pharmaceutique sous forme d'un précurseur et en ce que la substance active est formée par réaction chimique ou enzymatique à l'intérieur ou à l'extérieur du dispositif.

7. Un dispositif selon la revendication 6, caractérisé en ce qu'il contient, comme la forme de précurseur d'une substance active d'un point de vue pharmaceutique, des cellules vivantes, particulièrement des cellules de tissus connectifs.

8. Un dispositif selon l'une des revendications 1 à 6, caractérisé en ce que la substance active d'un point de vue pharmaceutique est une substance ayant une activité anti-bactérienne et/ou anti-toxique.

9. Un dispositif selon l'une des revendications 1 à 6, caractérisé en ce que la substance active d'un point de vue pharmaceutique est de la taurolidine.

10. Un dispositif selon l'une des revendications 1 à 9, caractérisé en ce qu'il contient de plus un dispositif de drainage tubulaire des plaies connecté de façon opérative pour drainer les sécrétions des plaies et les enlever des plaies et des cavités de plaies.

11. Un dispositif selon la revendication 10, caractérisé en ce que l'extrémité du dispositif de drainage tubulaire des plaies qui est situé dans le corps, est divisée en plusieurs filaments.

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FIG.1.

